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| 10/655,870 | 09/05/2003 | George D. Purvis III | 016939.0103 (03-52279-FAI | 7307 |

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| EXAMINER | |
|---|---|
| ZEMAN, MARY K | |
| **ART UNIT** | **PAPER NUMBER** |
| 1631 | |

DATE MAILED: 03/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/655,870 | PURVIS, GEORGE D. | |
| | Examiner | Art Unit | |
| | Mary K. Zeman | 1631 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/7/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-31 are pending in this application.

### *Information Disclosure Statement*

The IDS filed 4/7/04 has been entered and considered. An initialed copy of the PTO-1449 is included with this action.

### *Drawings*

The drawings were received on 1/27/04. These drawings are acceptable to the examiner.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1- 31 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to 1) a system which lacks any physical component, and recites simply data or program components; and lack a practical application 2) programs which lack a practical application and 2) methods which do not provide a concrete, tangible and useful result as required; and do not provide a practical application. Neither the system nor the methods achieve a physical transformation of one thing into another. The system does not produce any result that is concrete, tangible and useful. The "calculated repulsion term" identified by the method is not a concrete tangible and useful result as set forth in the guidelines for computer-implemented inventions. The result is an abstract idea which must be further manipulated or interpreted to be useful.

Further, there is no practical application of the abstract idea of the invention. The claims are all drawn to methods and systems for identifying a natural property of a protein-ligand complex. The "calculated repulsion term" is a description of a natural force between an atom pair. This is a description of a force which occurs in Nature, and the claims recite no practical application for

this term. The specification suggests the term may be useful in protein ligand design, however the claims are not limited in this fashion.

Claims directed to nothing more than abstract ideas (such as mathematical algorithms), natural phenomena, and laws of nature are not eligible and therefore are excluded from patent protection. Diehr, 450 U.S. at 185, 209 USPQ at 7; accord, e.g., Chakrabarty, 447 U.S. at 309, 206 USPQ at 197; Parker v. Flook, 437 U.S. 584, 589, 198 USPQ 193, 197 (1978); Benson, 409 U.S. at 67-68 , 175 USPQ at 675; Funk, 333 U.S. at 130, 76 USPQ at 281. "A principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented, as no one can claim in either of them an exclusive right." Le Roy, 55 U.S. (14 How.) at 175. Instead, such "manifestations of laws of nature" are "part of the storehouse of knowledge," "free to all men and reserved exclusively to none." Funk, 333 U.S. at 130, 76 USPQ at 281.

Thus, "a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter" under Section 101. Chakrabarty, 447 U.S. at 309, 206 USPQ at 197. "Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity." Ibid. Nor can one patent "a novel and useful mathematical formula," Flook, 437 U.S. at 585, 198 USPQ at 195; electromagnetism or steam power, O'Reilly v. Morse, 56 U.S. (15 How.) 62, 113-114 (1853); or "[t]he qualities of * * * bacteria, * * * the heat of the sun, electricity, or the qualities of metals," Funk, 333 U.S. at 130, 76 USPQ at 281; see Le Roy, 55 U.S. (14 How.) at 175.

To satisfy section 101 requirements, the claim must be for a practical application of the § 101 judicial exception, which can be identified in various ways:

1) The claimed invention "transforms" an article or physical object to a different state or thing.

2) The claimed invention otherwise produces a useful, concrete and tangible result, based on the factors discussed below.

Practical Application That Produces a Useful, Concrete, and Tangible Result

For eligibility analysis, physical transformation "is not an invariable requirement, but merely one example of how a mathematical algorithm [or law of nature] may bring about a useful application." AT&T, 172 F.3d at 1358-59, 50 USPQ2d at 1452... In determining whether the claim is for a "practical application," the focus is not on whether the steps taken to achieve a particular result are useful, tangible and concrete, but rather that the final result achieved by the

claimed invention is "useful, tangible and concrete." (1) "USEFUL RESULT" For an invention to be "useful" it must satisfy the utility requirement of section 101. The USPTO's official interpretation of the utility requirement provides that the utility of an invention has to be (i) specific, (ii) substantial and (iii) credible. MPEP § 2107 and Fisher, 421 F.3d at ___, 76 USPQ2d at 1230 (citing the Utility Guidelines with approval for interpretation of "specific" and "substantial"). (2) "TANGIBLE RESULT" The tangible requirement does not necessarily mean that a claim must either be tied to a particular machine or apparatus or must operate to change articles or materials to a different state or thing. However, the tangible requirement does require that the claim must recite more than a § 101 judicial exception, in that the process claim must set forth a practical application of that § 101 judicial exception to produce a real-world result. Benson, 409 U.S. at 71-72, 175 USPQ at 676-77 (invention ineligible because had "no substantial practical application."). "[A]n application of a law of nature or mathematical formula to a … process may well be deserving of patent protection." Diehr, 450 U.S. at 187, 209 USPQ at 8 (emphasis added); see also Corning, 56 U.S. (15 How.) at 268, 14 L.Ed. 683 ("It is for the discovery or invention of some practical method or means of producing a beneficial result or effect, that a patent is granted . . ."). In other words, the opposite meaning of "tangible" is "abstract." (3) "CONCRETE RESULT" Another consideration is whether the invention produces a "concrete" result. Usually, this question arises when a result cannot be assured. In other words, the process must have a result that can be substantially repeatable or the process must substantially produce the same result again. In re Swartz, 232 F.3d 862, 864, 56 USPQ2d 1703, 1704 (Fed. Cir. 2000) (where asserted result produced by the claimed invention is "irreproducible" claim should be rejected under section 101). The opposite of "concrete" is unrepeatable or unpredictable.

See also:
http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/guidelines101_20051026.pdf

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10, 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 31 recites various "means for" clauses. Claims 1-10 recite "modules" that have a certain function, and are described only by that function. The means for and "modules" lack specific related structures in the specification. No specific computer, apparatus, or system structures for performing these means are disclosed. See MPEP 2181: 35 U.S.C. 112, sixth paragraph states that a claim limitation expressed in means-plus-function language "shall be construed to cover the corresponding structure…described in the specification and equivalents thereof." "If one employs means plus function language in a claim, one must set forth in the specification an adequate disclosure showing what is meant by that language. If an applicant fails to set forth an adequate disclosure, the applicant has in effect failed to particularly point out and distinctly claim the invention as required by the second paragraph of section 112." In re Donaldson Co., 16 F.3d 1189, 1195, 29 USPQ2d 1845, 1850 (Fed. Cir. 1994) (in banc)... Whether a claim reciting an element in means- (or step-) plus-function language fails to comply with 35 U.S.C. 112, second paragraph, because the specification does not disclose adequate structure (or material or acts) for performing the recited function is closely related to the question of whether the specification meets the description requirement in 35 U.S.C. 112, first paragraph. See In re Noll, 545 F.2d 141, 149, 191 USPQ 721, 727 (CCPA 1976) (unless the means-plus-function language is itself unclear, a claim limitation written in means-plus- function language meets the definiteness requirement in 35 U.S.C. 112, second paragraph, so long as the specification meets the written description requirement in 35 U.S.C. 112, first paragraph)… the invocation of 35 U.S.C. 112, sixth paragraph, does not exempt an applicant from compliance with 35 U.S.C. 112, first and second paragraphs. See Donaldson, 16 F.3d at 1195, 29 USPQ2d at 1850; Knowlton, 481 F.2d at 1366, 178 USPQ at 493.

Claims 1-10, 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As set forth above, claims 21 recite various "means for" clauses. Claims 1-10 recite "modules" for performing functions. The specification as filed does not set forth specific

structures for performing the means recited. The means for and modules all lack specific related structures in the specification. See MPEP 2181: 35 U.S.C. 112, sixth paragraph states that a claim limitation expressed in means-plus-function language "shall be construed to cover the corresponding structure…described in the specification and equivalents thereof." "If one employs means plus function language in a claim, one must set forth in the specification an adequate disclosure showing what is meant by that language. If an applicant fails to set forth an adequate disclosure, the applicant has in effect failed to particularly point out and distinctly claim the invention as required by the second paragraph of section 112." In re Donaldson Co., 16 F.3d 1189, 1195, 29 USPQ2d 1845, 1850 (Fed. Cir. 1994) (in banc). One of skill in the art would not necessarily be apprised of the specific structures to be used in the claimed apparati.

Claims 1-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Further in claim 1, it is entirely unclear what the system comprises. No hardware of any sort is set forth in the claim and the specification does not set forth any particular definition for a system. Claim 1 merely requires a module capable of performing a particular calculation. The description of the module is further indefinite. What is the module accessing? What are "useable" parameters? Just because a parameter is useful in a process, it is not apparently required. The "useable" is not a positive active limitation of the claim and is merely an intended use thereof. How do the parameters "correspond" to an atom-pair type? How are the parameters "used" in the calculation? No particular calculation is set forth such that one of skill in the art would be apprised of the scope of the claimed systems. How is a repulsion term "useable" to calculate the PMF? How is it communicated, and to whom? The final limitation of "for calculation of the PMF score" is an intended use of the "calculated repulsion term", and is not an actual limitation of the claim.

Claims 2-5 all have similar issues with "corresponding". How does any parameter correspond with an "atom –pair"?

It is unclear how the system limitation of claim 5 further limits the system of claim 4.

The term "Best agreement" in claim 5 is a relative term which renders the claim indefinite. The term "best agreement" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The further limitations of claim 7 do not remedy this, as "determined according to a plurality of RMS deviations" does not actually describe what is a "best agreement".

It is unclear how the limitation of claim 6 which describes a publicly available database modifies the claimed system.

It is unclear how a manual process according to claim 9 is implemented in the system of the preceding claims.

It is entirely unclear how the limitation of claim 10 (the genetic algorithm) modifies the system of claim 9, or any preceding claim. The application of an entire type of mathematics is unclear without any particular limitation or direction. At what point and where in the system is a genetic algorithm applied?

Claims 11-20, 21-30 and 31 mirror claims 1-10 above. Each of the above rejections is applied similarly.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9, 11-19, 21-19, 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Muegge (1999).

The claims are drawn to methods, systems and programs for calculating a PMF score of a protein ligand complex. The claims use parameters such as minimum binding energy distance values and well-depth values to calculate a repulsion term which is then able to be used in PMF score calculation. The protein-ligand information can come from a protein data bank. The

calculated information can be compared with empirically derived data. Certain parts of the process can be done manually or automatically. The systems claims do not comprise any actual hardware, so any software with the requisite functionality meets the claim limitations.

Muegge et al. (J Med Chem 1999 42 :791 PTO-1449) discloses methods of scoring PMF for protein-ligand interactions. The methods of Muegge are all computer-implemented, and therefore meet the limitations for the systems and programs. Muegge discloses accessing one or more parameters from a protein data bank (Brookhaven). The parameters correspond to atom-pair type information, such as minimum energy distance values and depth values. The "method section" particularly at page 793, discloses the use of such parameters in the PMF scoring function. "$r$ is the atom pair distance... $f'_{Vol\text{-}corr}(r)$ is the ligand volume correction factor" etc. The volume correction factor appears to be the same as the "well depth value" of claim 3. Muegge states "the ratio between the volume occupied by protein atoms and solvent atoms affects the density and therefore the depth of the PMF for each atom-type pair (eq1)." See also the appendix for particular equations and theory. The calculated terms are then used to score a PMF. Known protein-ligand interactions were used to compare with the calculated results. Muegge specifically discusses the usefulness of the scoring of the PMF in docking algorithms, such as DOCK4, which is often used for ligand design strategy. As such, Muegge anticipates the rejected claims.

Claims 1-9, 11-19, 21-19, 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Mitchell et al. (1999).

Mitchell et al. (J Computational Chem 1999 20(11) 1165-1176) discloses methods of scoring PMF of protein ligand interactions (BLEEP). The methods of Mitchell are all computer-implemented, and therefore meet the limitations for the systems and programs. Mitchell discloses accessing one or more parameters from a protein data bank (Brookhaven). The data can be automatically or manually collected and curated. The parameters correspond to atom-pair type information, such as minimum energy distance values and depth values. Atom-type pair information is discussed at page 1167-1169; atom-pair type distance distributions are discussed at page 1169; wel-depth values are discussed at page 1171-1173. These parameters are used to

score a PMF for the protein ligand interaction at pages 1173-1174. Mitchell specifically discusses the use of the BLEEP program in the context of computer-aided drug design at page 1176. As such, Mitchell anticipates the rejected claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10, 20 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muegge as applied to claims 1-9, 11-19, 21-29 and 31 above, in view of Morris (1998)..

Claims 9, 20 and 30 each add the limitation that a genetic algorithm is used in the system, method or program. The limitation does not set forth how the genetic algorithm is to be used, or on what data.

As set forth above, Muegge et al. (J Med Chem 1999 42 :791 PTO-1449) discloses methods of scoring PMF for protein-ligand interactions. The methods of Muegge are all computer-implemented, and therefore meet the limitations for the systems and programs. Muegge discloses accessing one or more parameters from a protein data bank (Brookhaven). The parameters correspond to atom-pair type information, such as minimum energy distance values and depth values. The "method section" particularly at page 793, discloses the use of such parameters in the PMF scoring function. "$r$ is the atom pair distance… $f_{Vol\text{-}corr}(r)$ is the ligand volume correction factor" etc. The volume correction factor appears to be the same as the "well depth value" of claim 3. Muegge states "the ratio between the volume occupied by protein atoms and solvent atoms affects the density and therefore the depth of the PMF for each atom-type pair (eq1)." See also the appendix for particular equations and theory. The calculated terms are then used to score a PMF. Known protein-ligand interactions were used to compare with the calculated results. Muegge specifically discusses the usefulness of the scoring of the PMF in docking algorithms, such as DOCK4, which is often used for ligand design strategy.

Muegge does not teach the use of a genetic algorithm.

Morris et al. (J Computational Chem 1998 19(14) 1639-1662 ; PTO-1449) discloses methods of using genetic algorithms in docking programs to predict bound conformations of flexible ligands. Morris et al discuss the known methods of 3 dimensional protein-ligand analysis, which include the automated determination of minimized free energy conformations. Morris discusses known genetic algorithms (1641), and their use in docking programs. The genetic algorithm is used for searching the global computational space to identify a most fit structure of the protein-ligand interaction. The AUTODOCK program performs a specified number of dockings, then carries out conformational cluster analysis on the docked conformations to determine which are similar ranked by increasing energy. The "fitness" of the structure can be based on a variety of parameters. AUTODOCK uses a dispersion/repulsion term, a hydrogen bonding term, and a screened Coulombic electrostatic potential. MSMS is used to compute the analytical molecular surfaces, which discuss appears analogous to a well-depth value. Morris found their combination of the genetic algorithm with the free energy calculations and docking/design programs to provide faster and more reliable results.

It would have been prima facie obvious to one of ordinary skill in the art to apply the known computation methods of genetic algorithms to the methods of Muegge for scoring PMF functions of protein-ligand interactions. One of skill in the art would have been motivated to utilize the genetic algorithms as they provide faster and more successful searching of free energy conformations as shown by Morris et al. One of ordinary skill in the art would have had a reasonable expectation of success in such a combination, as the computational aspect of genetic algorithms were well known, and the AUTODOCK program was available at the time the invention was made. Therefore, the invention as a whole, would have been prima facie obvious, absent evidence to the contrary.

***Conclusion***

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Mitchell et al. (J Computational Chemistry 20(11) 1177-1185 (1999). This document further describes use of the BLEEP program.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (571) 272 0723

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, PhD can be reached on (571) 272 0718. The fax phone number for the organization where this application or proceeding is assigned is 571 273 8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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MARY K. ZEMAN
PRIMARY EXAMINER

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3/3/06